CLAIMS

1 - **A process** for the preparation of anhydrous active Pharmaceutical ingredients (API's), which are taxane derivatives, characterized which the hydrated taxane derivative is solubilized in a solvent that is chemically inert and forms an azeotrope with water, being that, the water of hydration is removed by azeotropic distillation at a temperature between -20 and 200°C and at a pressure between <0.001 and 780 mm Hg, resulting in the anhydrous compound with an amount of water inferior to 1.0% w/w.

2 - **A process** according to claim 1 characterized by obtaining anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) as a product.

3 - **A process** according to claim 2, characterized by employing the following steps:

(a) Solubilizing the hydrated (2R,3S) 4-acetoxy-2-α benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in a chemically inert sol vent which forms an azeotrope with water;

(b) Removal of the water of hydration by way of azeoptropic distillation at a temperature between -20 and 200°C and at a pressure between <0.001 and 780 mm Hg;

(c) Obtaining the anhydrous compound(2R,3S) 4-acetoxy-2-α benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), in which the water content is inferior to 1.0% w/w/.

4 - **A process** according to claim 3 characterized by the use of a solvent or a mixture of solvents in step a).

5 - **A process** according to claim 4 characterized by the fact that the solvent employed is an alcohol, an organic acid, a halogenated solvent, an aromatic solvent or other solvent, of sufficient polarity, to effect the solubilization of the hydrated product.

6 - **A process** according to claim 5 characterized by the fact that the solvent employed is a linear or branched chain alcohol.

7 - **A process** according to claim 3 characterized by the facts that in steps a) and b) the (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) is hydrated with between 1 to 20% water and the solvents employed are absolute ethanol and toluene in a relative proportion close to 1:9, at a temperature between 10 and 70°C and at a pressure between 10 and 100 mm Hg.

8 - **A process** for the preparation of anhydrous (2R,3S)4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) according to claims 1, 2, 3, 4, 5, 6, or 7, characterized by the fact that the product is obtained by the reaction between di-tertbutyl-dicarbonate (>99% purity) and N-desacetyl-N-debenzoyl paclitaxel (>98% purity), in equimolar quantities, employing an anhydrous solvent, which permits that, after removal of the solvent, it is possible to directly isolate in a pure and anhydrous form, (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-

β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I).

9 - **A process** according to claim 8 characterized by the fact that, the anhydrous solvent employed is an aliphatic or cyclic ether.

10 - **A process** according to claim 9 characterized by the fact that, the solvent employed is, preferentially, anhydrous tetrahydrofuran.

11 - **A process** for the preparation of anhydrous (2R,3S)4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) characterized by the fact that impure (2R,3S)4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) is subjected to the technique of purification by chromatography.

12 - **A process** according to claim 11 characterized by the fact that, the cromatographic technique employed is normal or reverse phase.

13 - **A process** according to claim 11 characterized by the fact that, a solvent or mixture of solvents is employed, recognizing the possibility of using the technique of gradient elution.

14 - **A process** according to claim 11 characterized by the fact that, a mixture of alkane and ester solvents is used, and that the stationary phase employed is either SiO_2 or Al_2O_3.

15 - **A process** according to claim 14 characterized by the fact that the mixture of solvents used consists, preferably,

of ethyl acetate and hexane in a proportion close to 20:80, changing gradually to a proportion of 80:20 and which the stationary phase employed is either SiO_2 or Al_2O_3 .

16 - **A process** according to claims 12 or 13 characterized by the fact that the mixture of solvents employed is a mixture of solvents consisting of methanol or acetonitrile and water or an aqueous buffer solution in the proportion close to 85:15, gradually changing to a proportion close to 75:25 and the stationary phase employed is a chemically modified silica gel.

17 - **A process**, characterized by the fact that a solvent is employed to effect the solubilization of the (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) which is capable of solubilizing, or is miscible with, between 3 and 200,000 molar equivalents of water; followed by mixture of the solution thus obtained with water, or water and a co-solvent, to induce crystallization, and, after crystallization, isolation and drying of the crystals of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate 3 H_2O (III) by conventional means.

18 - **A process**, according to claim 17 characterized by the fact that the solvent used to solubilize the (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) is polysorbate 80 and water is mixed with an alcohol containing between 1 and 8 carbons as a co-solvent.

19 - **A process**, according to claim 18 characterized by the fact that the solvent employed is polysorbate 80, and water is mixed with ethanol as the co-solvent.

20 - **A process**, according to claim 18 characterized by the fact that the solvent employed is polysorbate 80, and water is mixed with n-butanol as a co-solvent.

21 - **A process**, according to claim 17 characterized by the fact that the quantity of water employed is in the neighborhood of 2,000 molar equivalents relative to the quantity of the (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) utilized.

22 - **A process**, according to claim 21 characterized by the fact that the quantity of alcohol employed as a co-solvent is in the neighborhood of 60 molar equivalents relative to the quantity of the (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), employed.

23 - **A process**, according to claims 17, 18, 19, 20, 21 or 22 characterized by the fact that the final concentration of the (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), in polysorbate 80 is in the range of 0.025 to 0.067 mg/mL, preferably 0,04 g/mL, before admixture with water or water and co-solvent.

24 - **A process**, for the preparation of concentrated, sterile solutions of active pharmaceutical ingredients (API's), which are taxane derivatives characterized by the fact that a biocompatible vehicle, consisting of a solvent or mixture of solvents of sufficient polarity to effect complete solubilization of the active principle, chosen between water, ethanol, polyethoxylated sorbitol, lecithin or vegetable oils, is employed, a stabilizing agent such as an acid and/or antioxidant is added, and the resulting solutions are stable greater than or equal to 24 months when stored under an inert atmosphere at between 2 and 8°C.

25 - **A process**, according to claim 24 characterized by the fact that, the active ingredient is anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I).

26 - **A process**, according to claim 24 characterized by the fact that, the active ingredient is (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate 3 H_2O (III).

27 - **A process**, according to claim 24 characterized by the fact that, the active ingredient is 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-il (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II).

28 - **A process**, according to claim 24 characterized by the fact that polyethoxylated sorbitols are employed as the vehicle, preferably, polysorbate 80.

29 - **A process**, according to claim 28 characterized by the fact that the active principle, either anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate 3 H_2O (III), or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-il (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) is slowly added to the vehicle, to which has been previously added a stabilizing agent, with agitation, preferably, under an inert atmosphere, until complete solubilization of the active principle is achieved; and the solution thus obtained is filtered through a sterilizing membrane having a porosity less than or equal to 0.45 μm.

30 - **A process**, according to claim 28 characterized by the fact that either anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate 3 H_2O (III), or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-il (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) is slowly added to the vehicle, with agitation, preferably under an inert atmosphere, until complete solubilization of the active principle is achieved; a stabilizing agent is then added; and the solution thus obtained is filtered through a sterilizing membrane having a porosity less than or equal to 0.45 μm.

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31 - **A process**, according to claims 28, 29 or 30 characterized by the fact that a final concentration of anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate 3 H_2O(III), or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-il (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) between 1 and 100 mg/mL vehicle is obtained.

32 - **A process**, according to 31 characterized by the fact that the vehicle employed is polysorbate 80 and the concentration of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-il 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), on an anhydrous basis, is between 20 and 60 mg/mL, the concentration of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-il (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) is between 1 and 100 mg/mL and the sterilizing membrane employed has a porosity of 0.22 μm.

33 - **A process**, according to claim 32 characterized by the fact that the stabilizing agent employed is pharmaceutically compatible with the active ingredient and vehicle, has anti-oxidant properties and/or is capable of adjusting the pH of the formulation to between 3.0 and 6.5, preferably between 3.5 and 4.5.

34 - **A process**, according to claim 33, characterized by the fact that the stabilizing agent is an organic or inorganic acid, chosen among the following: aspartic, acetic, ascorbic, phosphoric, pyrophosphoric, hypophosphoric, hydrochloric, sulfuric, propionic, sorbic, erythorbic, caprylic, gallic, gluconic, benzoic, thiodipropionic, sulfurous (H_2SO_3) acids, a saturated fatty acid or an unsaturated fatty acid.

35 - **A process** according to claim 34 characterized by the fact that a combination of one or more stabilizing agents are employed.

36 - **A process**, according to claims 24 or 33 whereby the solvent employed is polysorbate 80 and the stabilizing agent is either acetic or ascorbic acid, or a combination thereof, added in sufficient quantity such that the pH of the resulting solution is between 3.5 to 4.5.

37 - **A pharmaceutical composition** containing anhydrous or hydrated taxane derivates, which is sterile, is stable for greater than or equal to 24 months when stored under an inert atmosphere at between 2 and 8°C, prepared according to the processes contained in claims 24 or 33 characterized by the fact that the solution obtained by these processes is filled in sterile, pyrogen free recipients for single or multiple use.

38 - **Use** of the compound obtained according to the process in claims 1 or 11, characterized by the fact that the compound is employed in the preparation of sterile and stable pharmaceutical compositions applicable to the treatment of disease or infirmity, such as neoplastic tumors and other conditions which respond to treatment with agents

that inhibit the depolymerization of tubulin, consisting of, cancers of the breast, ovaries, lungs and others.

39 - **Use** of the stable and sterile pharmaceutical composition according to the process in claims 24 or 33, characterized by the fact that the composition is employed in the preparation of medicaments applicable to the treatment of disease or infirmity, such as neoplastic tumors and other conditions which respond to treatment with agents that inhibit the depolymerization of tubulin, consisting of, cancers of the breast, ovaries, lungs and others.

40 - **Use** of the sterile and stable composition prepared according to the process in claims 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 characterized by the fact that the composition is utilized in the treatment of disease or infirmity, such as neoplastic tumors and other conditions which respond to treatment with agents that inhibit the depolymerization of tubulin, consisting of, cancers of the breast, ovaries, lungs and others.